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Tang, J., Liang, Y., O'Neill, C., Kee, F., Jiang, J., & Congdon, N. (2019). Cost-effectiveness and cost-utility of population-based glaucoma screening in China a decision-analytic Markov model. *The Lancet Global Health*, *7*(7), e968-e978. https://doi.org/10.1016/S2214-109X(19)30201-3

Published in:
The Lancet Global Health

Document Version:
Publisher's PDF, also known as Version of record

Cost-effectiveness and cost-utility of population-based glaucoma screening in China: a decision-analytic Markov model

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Summary

Background Glaucoma, particularly primary angle closure glaucoma (PACG), is a leading cause of global blindness. Nearly half of all people with PACG are of Chinese descent. Population-level glaucoma screening has generally not been found to be cost-effective in high-income countries; however, this assessment has rarely been done in low-income or middle-income countries. We aimed to assess the cost-effectiveness and cost-utility of population-level glaucoma screening in China.

Methods We developed decision-analytic Markov models for separate and combined screening for PACG and primary open angle glaucoma (POAG) to evaluate costs and benefits of community-level screening versus opportunistic case finding from a societal perspective. A cohort of individuals was followed in the model from age 50 years through a total of 30 1-year Markov cycles. Analyses were done separately for rural and urban settings. We did a meta-analysis of glaucoma prevalence studies in China to obtain prevalence estimates for PACG and POAG. Screening costs were taken from a Chinese screening programme and treatment costs from a tertiary Chinese eye hospital. Main outcomes were incremental cost-utility ratios (ICURs) using quality-adjusted life-years and incremental cost-effectiveness ratios (ICERs) using years of blindness avoided. We did one-way deterministic and simulated probabilistic sensitivity analyses to reflect uncertainty around ICURs and ICERs.

Findings Compared with no screening, combined screening of POAG and PACG in rural China is predicted to result in an ICUR of US$569 (95% CI 17 to 4180) and an ICER of $1280 (–58 to 7940), both of which are below the WHO cost-effectiveness threshold of one to three times rural gross domestic product. For the urban China setting, combined screening is predicted to result in fewer net costs and greater gain in health benefits than no screening. Findings were robust in all sensitivity analyses. Over 30 years, a total of 246 (95% CI 63 to 628) and 1325 (510 to 2828) years of blindness are predicted to be avoided for every 100 000 rural and urban residents screened, respectively.

Interpretation Population screening for glaucoma (POAG and PACG combined) is likely to be cost-effective in both urban and rural China. Future studies should investigate the effectiveness of interventions to improve acceptance of definitive care among people screened.

Funding Ulverscroft Foundation, Wenzhou Medical University Research Fund, Zhejiang Province Health Innovation Talents Project, and Wenzhou's Ten Major Livelihood Issues 2015.

Lancet Glob Health 2019; 7: e968–78

Published Online May 20, 2019 http://dx.doi.org/10.1016/S2214-109X(19)30201-3

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Introduction

Glaucoma is a leading cause of global blindness, affecting 64·3 million people worldwide in 2013, of whom a sixth dwell in China.[1,2] Nearly half of all people with primary angle closure (PAC) glaucoma (PACG) are of Chinese descent.[3] Although glaucoma can progress to blindness, it is generally asymptomatic in its early stages, when treatment is most effective. This makes early detection crucial to reduce the risks of visual impairment.[4] Screening programmes might be of particular value in rural settings, where population studies suggest that less than 50% of cases of PACG and less than 10% of cases of primary open angle glaucoma (POAG) are diagnosed.[5] Among those who are diagnosed, glaucoma has already caused severe damage in the majority.[6] However, several studies have reported that population-based glaucoma screening programmes are not cost-effective in high-income countries such as the UK[7,8] and Finland.[9]

We believe that glaucoma screening might be cost-effective in a Chinese setting for two reasons. First, when compared with other ethnic groups, people of Chinese descent have a two to four times higher prevalence of PACG.[10] The risk of blindness at diagnosis is up to four times higher for PACG than for POAG, which is the more common type of glaucoma among those of European descent.[11] Second, screening is likely to be less expensive in China, due in large part to lower labour costs as compared with high-income countries.[12]

To the best of our knowledge, no studies have investigated whether population-based glaucoma screening is cost-effective in China. The only cost-effectiveness study[13] of glaucoma screening in an Asian population found that

Research in context

Evidence before this study

PubMed, MEDLINE, CNKI, and Embase were searched for cost-effectiveness studies of glaucoma screening published in English or Chinese up to Oct 1, 2018, using the terms "glaucoma" AND "screening" OR "detection" AND "economic modelling" OR "cost-effectiveness" OR "cost-benefit" OR "cost-utility". Our search identified eight studies. A 2008 systematic review identified four studies on the cost-effectiveness of glaucoma screening published before 2005 and concluded that all these studies featured methodological weaknesses and outdated screening technology and treatments, providing insufficient evidence on which to base policy recommendations. The studies we identified published from 2005 onwards included studies in the UK, the USA, and Finland, which focused on screening solely for primary open angle glaucoma (POAG), the most prevalent type of glaucoma in these countries. These studies reported that population-based glaucoma screening programmes are not cost-effective in these high-income countries. The only cost-effectiveness study of glaucoma screening in an Asian population found that screening is highly cost-effective in India. However, a one-time decision analysis was used, which failed to capture the complexity of glaucoma progression in a temporally explicit fashion.

Added value of this study

The scenario of combined primary angle closure glaucoma (PACG) and POAG screening is likely to be cost-effective in the rural setting (incremental cost-effectiveness ratio US$1280, 95% CI −58 to 7940; incremental cost-utility ratio $569, 95% CI 17 to 4180) and dominates no screening in the urban setting. A total of 246 years (95% CI 63 to 628) of blindness would be avoided for every 100 000 rural residents screened and 1325 years (510 to 2828) for every 100 000 urban residents screened.

Implications of all the available evidence

Our finding that glaucoma screening is cost-effective in a large country like China could be of great importance to policy makers and programme planners. Previous conclusions that glaucoma screening is not cost-effective have been based on assumptions that apply more to high-resource settings—where most such research has been done—than low-income and middle-income countries such as China. This novel finding in China might result from a combination of lower screening costs and higher risk of eventual blindness in the absence of such programmes in the Chinese setting compared with high-income countries. It is also likely that the greater cost-effectiveness of screening for PACG, far more prevalent in China than in European-derived populations, plays an important role.

See Online for appendix

screening is highly cost-effective in India. However, a one-time decision analysis was used, which failed to capture the complexity of glaucoma progression in a temporally explicit fashion, and applicability of this result to the population of China is clearly uncertain due to differences in disease profile and health-care systems in the two countries.

To fill this evidence gap, we aim to provide evidence-based policy recommendations by building a comprehensive and dynamic decision-analytic Markov model incorporating the transition between various disease stages across time and providing for a robust estimate of the cost-effectiveness of population screening for glaucoma in China. This model is informed by a large number of glaucoma prevalence studies done in China and includes screening and treatment costs obtained from an actual glaucoma screening programme and a tertiary referral eye hospital in China. For illustrative purposes, we analysed rural and urban settings separately because they are expected to differ in terms of glaucoma prevalence[14,15] and access to and compliance[16] with health treatments.

Methods

Model overview

TreeAge Pro (TreeAge Software; Williamstown, MA, USA) was used to build Markov models monitoring the transition between discrete health states and the effects of prescribed interventions on transition probabilities. Three Markov models were built to describe separate screening for PACG and POAG and simultaneous screening for both conditions together (appendix). The latter is the most likely screening scenario but we felt it would be useful to understand the separate effects of the two diseases on combined screening, as approaches to screening differ somewhat. Analysing the two disease processes separately provides additional information potentially relevant to other low-resource settings where only one condition (such as POAG for African and Africa-derived populations) prevails. However, we acknowledge that there are additional benefits that arise as a result of screening both diseases; therefore, there might be some underestimation of cost-effectiveness in the separate screening scenarios.

A cohort of individuals was followed in the model from age 50 years through a total of 30 1-year Markov cycles.[17] Individuals were allowed to enter as healthy (free from glaucoma) or unhealthy (affected by glaucoma) and could transition to death from any health state. The Markov model for POAG was based on the International Society of Geographical and Epidemiologic Ophthalmology (ISGEO) glaucoma classification, which comprises five stages in addition to normal vision: mild POAG, moderate POAG, severe POAG, POAG-related unilateral blindness, and POAG-related bilateral blindness.[18] Each stage has a probability of progression to the next stage, but due to the nature of the disease, the model does not permit regression to an earlier stage even with treatment. The ISGEO classification of PACG was used, also encompassing five stages besides normal vision: PAC suspect, PAC, PACG without blindness, PACG-related unilateral blindness, and PACG-related bilateral blindness.[18] For both PACG and POAG, the risk of progression from one state to the next was reduced by various types of treatment, with the amplitude of reduction based on available published data.

Glaucoma prevalence

Prevalence studies specific to China have typically reported separate prevalence for POAG and PACG. We reviewed population-based studies on glaucoma prevalence done among Chinese populations by searching PubMed, MEDLINE, and Embase for articles published in English appearing after the initiation of the ISGEO diagnostic criteria in 2002, using the following combined terms: "glaucoma" AND "prevalence" OR "epidemiology" AND "China" OR "Chinese". We identified ten studies, among which seven (five in rural and two in urban settings, comprising a total of 22 070 participants) reported prevalence of PACG and eight (five rural and three urban, comprising 24 598 participants) reported prevalence of POAG (appendix). After appraising them using the frameworks of Boyle[19] and Morris,[20] prevalence data were quantitatively synthesised by means of a random-effects meta-analysis[21] processed in R version 3.5.1 (appendix). Prevalence of each ISGEO stage of POAG and PACG among people aged 50 years or older was synthesised separately for rural and urban settings. Because of insufficient data, it was inappropriate to provide separate prevalence estimates for bilateral POAG blindness for rural and urban areas and so a single estimate was provided for both. We used data from a glaucoma screening programme of 27 144 participants in Wenzhou, China,[6] that was carried out by a coauthor (YL) between March, 2014, and September, 2015, to estimate the proportion of patients with POAG with mild disease as 36·8%, moderate disease as 35·9%, and severe disease as 27·3%.

Our meta-analysis of prevalence studies indicated that 49% of people with PACG in rural areas and 74% of those in urban areas had been previously diagnosed and treated, compared with only 7% and 10% of people with POAG (appendix). Based on the assumption that the proportion of people with previously diagnosed POAG would differ by severity, we assumed that 1·8% of rural patients with mild POAG, 3·2% of those with moderate POAG, and 17·9% of those with severe POAG had been treated previously. The comparable figures in the urban setting were 2·6%, 4·9%, and 26·7%, respectively. The percentage of people with asymptomatic stages of PACG (ie, PAC and PAC suspect) being opportunistically diagnosed was assumed to be zero for both rural and urban settings.

Transition probabilities

All transitions from one health state to another take place in a 1-year cycle. Whenever possible, data on all relevant parameters were obtained from published studies or data sources specific to China, which we obtained by searching PubMed, MEDLINE, CNKI, and Embase for studies on glaucoma progression published in English or Chinese, using the following combined terms: "glaucoma" AND "incidence" OR "transition" OR "progression" AND "China" OR "Chinese". However, few data are available on the transition probabilities from one stage to the next stage without treatment intervention for Chinese patients with glaucoma. Therefore, these transition probabilities were inferred from studies done in other Asian countries, those having Chinese or closely related populations (such as Mongolia) being preferred (appendix). If Asian data were not available, we used transition probabilities estimated from other regions. In studies where multi-year rather than 1-year glaucoma incidence was reported, the 1-year incidence was calculated using the formula $r=-\log(1-p)/t$, where r denotes the 1-year incidence and p represents the cumulative incidence over length of interval t.[22] Transition probabilities between stages of glaucoma after medical treatments were also based on published studies done in Asian countries, such as Mongolia and Singapore, or from unpublished data sources.

Screening and intervention costs

Screening costs were calculated on the basis of the Wenzhou glaucoma screening programme (table 1).[6] These included costs for screening equipment and labour costs for medical personnel. All figures were collected in Chinese yuan but were converted into US dollars at an exchange rate of 6·79 yuan per dollar. The total cost per person for PACG screening was \$2·52 (appendix)

	Treatment costs per person for the first year (US\$)	Annual medication costs per person in follow-up years (US\$)
Screening and examination costs*		
Screening PACG	2·52	NA
Screening POAG	3·20	NA
Combined screening	3·20	NA
Full ophthalmological examination at a hospital	15·9	NA
Treatment costs		
PAC suspect	105	1·77
PAC	105	1·77
PACG	600	10·6
Mild POAG	256	256
Moderate POAG	345	230
Severe POAG	345	230
Unilateral blindness	6380	1080
Bilateral blindness	8920	3600

Costs are given to 3 significant figures. NA=not applicable. PACG=PAC glaucoma. POAG=primary open angle glaucoma. PAC=primary angle closure. *Detailed calculations on screening costs can be found in the appendix.

Table 1: **Screening cost and medical cost of treating glaucoma of different stages**

whereas the figure for POAG was slightly higher at \$3·20 due to the need for additional equipment.

In China, patients usually pay for medical service at hospitals, the cost of which might be partially reimbursed by medical insurance. We considered the societal costs of medical care, so specific reimbursement rates were not relevant. The costs we used are the amounts charged for medical care provided by the Affiliated Eye Hospital of Wenzhou Medical University—an urban, tertiary-level centre serving a population of 9 million. A proposed screening programme would reach out to local rural and urban communities, and participants who screen positive after preliminary examinations would be referred to local hospitals for further examination (see appendix for pathways for both organised screening and opportunistic case detection). Following such preliminary community screening, all people with suspected glaucoma were assumed to be referred to local hospitals for a definitive ophthalmic examination including gonioscopy, slit-lamp examination of the anterior and posterior segment, fundus photography (Canon CR-2 Digital Retinal Camera; Canon, Tokyo, Japan; NIDEK Non-Mydriatic AFC-330 auto fundus cameras; NIDEK, Tokyo, Japan), and automated perimetry (Humphrey750i; Carl Zeiss Meditec, Dublin, CA, USA). Those diagnosed with glaucoma were assumed to receive routine clinical care appropriate for the severity of glaucoma. Medications were assumed to be prescribed to patients with mild POAG. Patients with severe or moderate POAG or PACG were assumed to be treated by trabeculectomy, followed by postoperative medications for 6 weeks. Among them, 20% were assumed to fail the surgery and need long-term topical medical therapy.[23–26] Patients with PAC suspect or PAC were assumed to be treated by laser peripheral iridotomy with 10% of laser-treated patients also needing glaucoma mediation.[27]

The costs for the medications and surgeries (table 1) were obtained from the tertiary hospital mentioned above. These costs are controlled by the Chinese Government and vary little between institutions at the same level of the health-care system. The annual economic burden per bilaterally blind patient used in our model (\$8920) consisted of 53·2% direct medical costs, 6·4% direct non-medical costs, and 40·4% indirect costs.[28] The latter consists of loss of labour resources, loss of productivity among carers (usually family members), and modification costs. We assumed that the total cost for the initial year of bilateral blindness was \$8920 and that blind patients incurred only indirect costs (ie, \$3600) in subsequent years until death. Because people with unilateral blindness experience fewer productivity losses and require fewer care services compared with people with bilateral blindness, the indirect cost of unilateral blindness was assumed to be 30% of that for bilateral blindness, leading to an estimate of \$6380 for the initial year of unilateral blindness and \$1080 in subsequent years.

Compliance

Compliance in community-level screening was estimated by synthesising compliance data reported in those previous prevalence studies that offered similar free ophthalmologic examinations in China. Our meta-analysis showed that 86% of eligible adults from rural areas and 80% from urban areas participated in community screening (table 2). Compliance with referral to the base hospital for further testing among patients informed they had signs of glaucoma was assumed to be 19% and 57% among rural[16] and urban[6] residents, respectively. Compliance with topical medical therapy was assumed to be 75% and 60% in the urban[39] and rural[38] settings. Acceptance of recommended trabeculectomy surgery among patients diagnosed with PACG was 91% and 80% in the urban[36] and rural[15,29,30,32] settings, respectively. Compliance with laser peripheral iridotomy was assumed to be 78%[27] and 32%,[37] respectively, among urban and rural patients diagnosed with either PAC or PAC suspect.

Screening sensitivity and specificity

Sensitivity (95·3%) and specificity (34·0%) of the proposed outreach community screening for PACG only are based on a screening examination including the van Herick test with a cutoff of no more than 40% anterior chamber depth for the limbal angle, as reported in a population-based screening programme in China.[43] The sensitivity (64·0%) and specificity (95·0%) for optic nerve photographs are used in modelling the accuracy of POAG screening.[44] In the combined screening scenario, the sensitivity (98·3%) and specificity (32·3%) in the detection of PACG are based on combined sensitivities and specificities of the van Herick test and optic nerve photography.

Utilities and quality-adjusted life-years

To calculate quality-adjusted life-years (QALYs), we estimated utilities for each glaucoma stage. Some early stages of glaucoma, such as PAC suspect and PAC, are asymptomatic, so the utilities for the three health states were assumed equal to the full utility of a person free from glaucoma. Utilities were assumed to be 0·80 for people with mild POAG, 0·75 for those with moderate POAG, and 0·71 for those with severe POAG.[7] Following results in the Handan Eye Study,[40] patients with PACG without blindness were assumed to have a utility value of 0·75, whereas patients with unilateral and bilateral blindness were assumed to have utility values of 0·47 and 0·26, respectively.[41]

Other parameters

We used the natural age-specific mortality rates reported by Zhang and Wei.[45] Mortality rates were also allowed to depend on glaucoma severity with increased odds of mortality for people with mild and moderate POAG,[46] PACG without blindness,[46] and unilateral and bilateral blindness (table 2).[47] Following the National Institute for Health and Care Excellence (NICE) recommendations,[42] both costs and health state utilities were discounted at 3·5% per annum in the base-case analysis. In terms of cost-effectiveness threshold, WHO defines a health intervention as being very cost-effective if it costs less than the per-capita gross domestic product (GDP) for a given country and as cost-effective if it costs less than three times the per-capita GDP.[48] The per-capita GDP stratified for China's rural and urban areas was not directly available but were calculated to be $4010 and $10 800, respectively, inferred from the overall per-capita national GDP ($7950), urbanisation rate, and the urban–rural ratio (2·72) of per-capita disposable income.[49]

Outcomes

Main outcomes were incremental cost-utility ratios (ICURs) and incremental cost-effectiveness ratios (ICERs), calculated as the difference in the total costs between the screened and unscreened cohorts, divided by the difference in the total QALYs between the two cohorts (ICURs) or by the years of blindness avoided between the two cohorts (ICERs). Differences were calculated as values for the screened cohort minus values for the unscreened cohort. Positive ICURs and ICERs show the incremental costs required for increasing 1 QALY or avoiding 1 year of blindness per person, respectively. Negative ICURs and ICERs (regarded as dominating) indicate that screening results in fewer costs while increasing QALYs or avoiding additional years of blindness than does no screening. A half-cycle correction[50] was applied to both costs and benefits. Reporting of methods and results conform to the Consolidated Health Economic Evaluation Reporting Standards (appendix).[51]

Sensitivity analysis

To reflect the uncertainty around ICURs and ICERs, both one-way deterministic and simulated probabilistic sensitivity analyses were done. Differential discounting was used in the sensitivity analysis such that costs were discounted by 3·5% per annum and health state utilities by 1·5%.[42] The 95% CIs from the meta-analyses of glaucoma prevalence were used as the upper and lower bounds of the one-way deterministic sensitivity analysis.[52] A change of either 20% or 50% of the original values of the other parameters was used, depending on the uncertainty of the base-case parameters (appendix).[53] Additional sensitivity analyses were done by varying glaucoma-related mortality, indirect costs from blindness, and opportunistic detection rate of PAC and PAC suspect. Tornado diagrams were produced showing the five factors to which the ICURs were most sensitive. For the probabilistic sensitivity analysis, a beta distribution was assigned to prevalence and transition probabilities, a log-normal distribution to odds ratios, and a gamma distribution to cost parameters.[54] The upper and lower bounds used in the one-way probabilistic sensitivity

	Values	Source
Compliance with community screening		
Rural setting	86%	Liang et al,[29] Qu et al,[30] Zhong et al,[31] Song et al,[32] Sun et al[33]
Urban setting	80%	He et al,[14] He et al,[34] Wang et al[35]
Compliance with comprehensive hospital examination		
Rural setting	18·9%	Wang et al[16]
Urban setting	56·9%	Liang et al[6]
Compliance with trabeculectomy among patients with PACG and moderate and severe POAG		
Rural setting	80%	Liang et al,[29] Qu et al,[30] Song et al,[32] Pan et al[15]
Urban setting	91%	Sun et al[36]
Compliance with laser therapy among patients with PAC and PAC suspect		
Rural setting	32%	Thomas et al[37]
Urban setting	78%	Jiang et al[27]
Compliance with medication		
Rural setting	60%	Li et al[38]
Urban setting	75%	Lui et al[39]
Utilities		
No disease	1·00	Assumption
Mild POAG	0·80	Burr et al[7]
Moderate POAG	0·75	Burr et al[7]
Severe POAG	0·71	Burr et al[7]
PAC suspect	1·00	Assumption
PAC	1·00	Assumption
PACG	0·75	Sun et al[40]
Unilateral blindness	0·47	Brown et al[41]
Bilateral blindness	0·26	Brown et al[41]
Discount rate for costs and benefits (base-case analysis)	3·5%	NICE[42]
Discount rate for benefits (sensitivity analysis)	1·5%	NICE[42]
Sensitivity at community screening		
PACG only	95·3%	Zhang et al[43]
POAG only and in combined screening	64·0%	Maa et al[44]
PACG in combined screening	98·3%	Zhang et al,[43] Maa et al[44]
Specificity at community screening		
PACG only	34·0%	Zhang et al[43]
POAG only and in combined screening	95·0%	Maa et al[44]
PACG in combined screening	32·3%	Zhang et al,[43] Maa et al[44]
Mortality rates by age group, years		
50–54	0·364%	Zhang and Wei[45]
55–59	0·518%	Zhang and Wei[45]
60–64	0·854%	Zhang and Wei[45]
65–69	1·421%	Zhang and Wei[45]
70–74	3·149%	Zhang and Wei[45]
75–79	4·861%	Zhang and Wei[45]
80–84	8·932%	Zhang and Wei[45]
Increased mortality risk for different groups, odds ratio		
People with mild, moderate, or severe POAG	1·8	Xu et al[46]
People with PACG but not blindness	3·1	Xu et al[46]
People with unilateral or bilateral blindness	3·9	Li et al[47]

Values and sources are the same for both urban and rural settings unless otherwise specified. PACG=PAC glaucoma. POAG=primary open angle glaucoma. PAC=primary angle closure. NICE=National Institute for Health and Care Excellence.

Table 2: **Estimates for compliance, utility, mortality, and other parameters**

	Costs per person, $	QALYs per person	Incremental costs per 100 000 people screened, $	Incremental QALYs (95% CI) per 100 000 people screened	ICURs (95% CI), $	Years of blindness per person	Years of blindness avoided per 100 000 people screened	ICERs (95% CI), $
Rural setting								
PACG								
No screening	386	16·23	..	..	..	0·18091	..	..
Screening	387	16·23	149 000	512 (172 to 1849)	290 (−390 to 1840)	0·17879	212 (72 to 702)	670 (−823 to 4570)
POAG								
No screening	153	16·44	..	..	..	0·06795	..	..
Screening	157	16·44	456 000	30 (7 to 76)	15 000 (7020 to 50 500)	0·06766	29 (5 to 80)	15 600 (6940 to 68 200)
Combined								
No screening	522	16·02	..	..	..	0·024608	..	..
Screening	525	16·03	313 000	551 (115 to 1398)	569 (17 to 4180)	0·024363	246 (63 to 628)	1280 (−58 to 7940)
Urban setting								
PACG								
No screening	347	16·20	..	..	..	0·015413	..	..
Screening	334	16·24	−1 288 000	3940 (1197 to 8032)	Dominating	0·014281	1132 (343 to 2425)	Dominating
POAG								
No screening	200	16·37	..	..	..	0·08632	..	..
Screening	212	16·38	1 219 000	135 (41 to 298)	9060 (4700 to 20 400)	0·08469	162 (40 to 335)	7510 (3860 to 22 000)
Combined								
No screening	533	15·93	..	..	..	0·23723	..	..
Screening	526	15·98	−701 000	4193 (1407 to 8563)	Dominating	0·22398	1325 (510 to 2828)	Dominating

Costs are given in US dollars. Costs, QALYs, and years of blindness are lifetime values per person, whereas incremental costs, incremental QALYs, ICURs, years of blindness avoided, and ICERs are calculated against the no screening scenario per 100 000 people screened. Negative ICURs and ICERs are regarded as dominating. QALY=quality-adjusted life-year. ICUR=incremental cost-utility ratio. ICER=incremental cost-effectiveness ratio. PACG=primary angle closure glaucoma. POAG=primary open angle glaucoma.

Table 3: **Base-case cost-utility and cost-effectiveness results from glaucoma screening compared with no screening for rural and urban settings**

analysis were used to define the distribution parameters. Probabilistic uncertainty was evaluated by recalculating ICERs for 10 000 random draws from the probability distribution of each parameter.[53,55] The percentile-based non-parametric bootstrap method[56] was used to calculate the 95% CIs for the ICURs and ICERs.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The cost-utility analysis shows that programmatic screening for PACG but not POAG dominated no screening in the urban setting (table 3). In the rural setting, screening for PACG required extra financial investment but was still likely to be cost-effective (ICUR $290, 95% CI −390 to 1840). POAG screening in the urban setting compared with no screening gained 1 QALY at a cost of $9060 (95% CI 4700 to 20 400), satisfying the criterion for a highly cost-effective health intervention. However, POAG screening in rural areas yielded an ICUR of $15 000 (7020 to 50 500), which is approximately 3·7 times of rural GDP. When screening for both POAG and PACG simultaneously, as would usually be the case in practice, screening dominated no screening in the urban setting and the ICUR for the rural setting was $569 (17 to 4180), again suggesting that a screening programme is likely to be cost-effective in both settings.

Parallel to the cost-utility analysis, the cost-effectiveness analysis showed that screening for PACG alone resulted in fewer costs and decreased years of blindness than did no screening in the urban setting (table 3). In the rural setting, such screening would avoid 1 year of blindness at an ICER of $670 (95% CI −823 to 4570). Screening for POAG in rural areas avoided 1 year of blindness at a cost of $15 600 (6940 to 68 200), which was approximately 3·9 times the rural per-capita GDP. By contrast, POAG screening in urban areas yielded an ICER of $7510 (3860 to 22 000) per year of blindness avoided and was thus likely to be cost-effective. Finally, a scenario of combined PACG and POAG screening dominated no screening in the urban setting and was likely to be cost-effective (ICER $1280, 95% CI −58 to 7940) in the rural setting. With such a screening programme, over the 30-year time horizon investigated in the model an estimated 246 years (95% CI 63 to 628) of blindness would be avoided for every 100 000 rural residents screened and 1325 years (510 to 2828) avoided for every 100 000 urban residents screened, commencing at age 50 years. Subgroup analysis

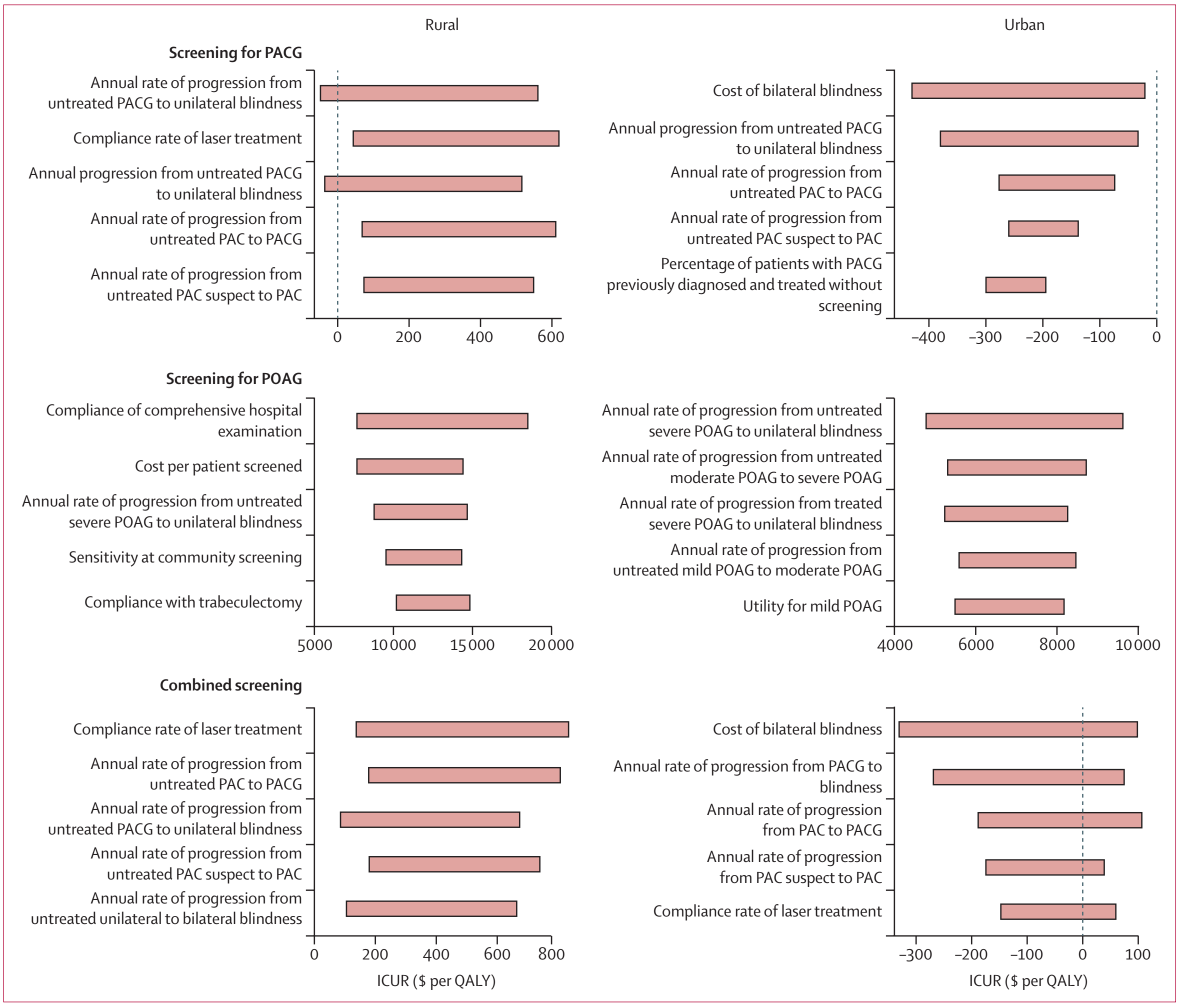

Figure: **Deterministic one-way sensitivity analysis**
Costs are given in US dollars. Analysis is done on the five parameters that caused the largest changes to the ICUR in each screening combination in different settings. The intervention was defined as cost-effective if it cost less than $12 030 in rural areas (per-capita GDP $4010) and less than $32 000 in urban areas (per-capita GDP $10 800). GDP=gross domestic product. ICUR=incremental cost-utility ratio. PAC=primary angle closure. PACG=PAC glaucoma. POAG=primary open angle glaucoma.

shows that combined screening in the rural setting is cost-effective for all age groups (appendix).

For the scenario of screening for PACG only and the combined strategy screening for both POAG and PACG, the base-case results were insensitive to uncertainty over a broad range of parameter values that we specified in the model, with all screening scenarios consistently dominant or within one-times per-capita GDP (figure). Threshold analysis showed that combined screening stopped being cost-effective if screening cost per person was more than $34·2 in rural areas (11 times the actual cost of the model screening programme used in our estimates) and more than $558 in urban areas (174 times the actual cost), based on a willingness-to-pay threshold of three-times per-capita GDP. For POAG screening, varying the parameters caused the ICUR to exceed the cost-effectiveness threshold of three-times per-capita GDP for the rural setting but not the urban setting (figure). Model results were robust to several additional sensitivity analyses, varying glaucoma-related mortality, indirect costs from blindness, and the percentage of PAC and PAC suspect being opportunistically diagnosed (appendix).

Probabilistic sensitivity analysis showed that the base-case ICUR and ICER were robust to randomly distributed parameters (appendix). PACG screening in rural areas dominated no screening in 18·9% of the simulations and did not dominate yet remained cost-effective in the remaining 81·1%. Likewise, in the urban setting, PACG screening dominated no screening in 89·3% of simulations and was cost-effective in the remaining 10·7%. Screening for POAG but not PACG was unlikely to be cost-effective in the rural setting because the ICUR exceeded the cost-effectiveness criterion of three-times per-capita GDP in 76·4% of simulations. By contrast, there was only 0·3% chance that screening in urban areas for POAG was not cost-effective. Finally, when both

	Rural setting					Urban setting					Comparison screening interval for ICER calculation
	Years of blindness per person	Costs per person, $	Years of blindness avoided per 100 000 people screened	Incremental costs per 100 000 people screened, $	ICERs, $	Years of blindness per person	Costs per person, $	Years of blindness avoided per 100 000 people screened	Incremental costs per 100 000 people screened, $	ICERs, $	
Imperfect compliance (base case)											
One-off	0·24363	525·0	..	..	..	0·22398	526·1	..	..	..	..
10 years	0·23870	530·8	493	585 000	1190	0·20776	528·3	1622	224 000	138	One-off
5 years	0·23280	538·5	590	769 000	1300	0·19212	531·5	1564	316 000	202	10 years
3 years	0·22601	547·8	679	925 000	1360	0·17944	537·4	1268	594 000	469	5 years
2 years	0·21881	558·1	720	1 035 000	1440	0·17006	545·8	938	838 000	894	3 years
1 year	0·20317	584·5	1564	2 637 000	1690	0·15774	570·5	1232	2 471 000	2010	2 years
Assumption of perfect compliance											
One-off	0·21220	509·1	..	..	..	0·20112	510·2	..	..	..	..
10 years	0·18143	504·5	3077	457 000	149	0·17163	511·8	2949	156 000	53	One-off
5 years	0·16896	516·2	1247	1 165 000	934	0·15829	525·4	1334	1 359 000	1020	10 years
3 years	0·16373	531·3	523	1 512 000	2890	0·15237	541·5	592	1 609 000	2720	5 years
2 years	0·16110	546·0	263	1 465 000	5570	0·14930	556·6	307	1 512 000	4920	3 years
1 year	0·15848	578·0	262	3 201 000	12 000	0·14613	588·7	317	3 209 000	10 100	2 years

Costs are given in US dollars. Years of blindness and costs are lifetime values per person screened whereas years of blindness avoided, incremental costs, and ICERs are calculated per 100 000 people screened against the previous screening interval scenario. 95% CIs for ICERs are presented in the appendix (p 21). ICER=incremental cost-effectiveness ratio.

Table 4: **Cost-effectiveness of combined screening with varied compliance levels and screening intervals**

POAG and PACG were simultaneously screened, screening rural and urban residents was cost-effective in 99·9% and 100·0% of simulations, respectively.

In both rural and urban settings, more frequent screening avoided more years of blindness (table 4). In the base case, the best scenario was annual screening, which yielded the largest health benefits with required additional costs within the WHO very cost-effective threshold (table 4). When compliance with screening, laser, and medical treatments was assumed to be perfect, annual screening in rural areas was close to the cost-effective threshold and screening every 2 years was the best strategy (table 4). By contrast, annual screening in urban areas might still be consistently cost-effective, even with perfect compliance.

Discussion

Our study suggests that combined screening for POAG and PACG in China is likely to be cost-effective, apparently due to the relatively low costs of screening, particularly labour costs, and the high risk of blindness in untreated cases, particularly those with PACG. Such screening in China is likely to fulfil WHO's criteria[57] for population screening: the natural history of glaucoma is adequately understood, early asymptomatic glaucoma stages are recognisable, screening is acceptable to the population, labour costs are low, and facilities for diagnosis and treatment are reasonably available.

We compared our results with previous studies. Our finding that a hypothetical screening for POAG (but not PACG) for individuals aged 50 years or older is not cost-effective in rural areas accords with studies on European-derived populations where POAG is by far the most prevalent form of glaucoma. For instance, the incremental cost of 1 QALY gained by a POAG screening programme in Finland was found to be $38 300, which fell below the cost-effectiveness threshold.[9] However, due to uncertainty in the prevalence of glaucoma, the probabilistic sensitivity analysis of this result showed that screening might not be cost-effective in 29% of simulated cases. Screening for POAG in the UK resulted in an ICER above the threshold of £30 000 ($39 800) over a broad range of assumed POAG prevalences (1% to 10%).[7] This result might have been due to a combination of higher screening costs and lower savings in a high-resource environment where POAG—the type less likely to lead to blindness—predominates and many patients would be detected in non-screening settings such as during routine glasses checks. In a more recent study[8] on the worth of doing a randomised controlled trial on glaucoma screening in the UK, it was found to be unlikely to be worthwhile and resulted in an ICER that was three to four times the NICE recommended threshold. In the USA, routine patient-initiated ophthalmologic assessments might be cost-effective ($46 000 per QALY) but the results were sensitive to assumptions.[58] As a result of this evidence, multiple bodies of academics, policy makers, and programme planners, including the US Preventive Healthcare Task Force,[59] the Royal College of Ophthalmologists,[60] and the American Academy of

Ophthalmology,[61] have concluded either that glaucoma screening is not cost-effective or that evidence is insufficient to conclude on its cost-effectiveness. None of these policy statements has recommended glaucoma screening in the general population. Regarding glaucoma screening in lower-income and middle-income countries, a population-based screening programme has been shown to be cost-effective in India.[13] However, this analysis used a static decision-analytic model that was primarily concerned with one-time treatment costs and thus it was not possible to consider lifetime costs, nor the transitions among different glaucomatous states, as rigorously as in the present study.

Our finding in a careful and well informed analysis that glaucoma screening is cost-effective in a large country like China is of potentially great importance to policy makers and programme planners. The published literature is in wide agreement that glaucoma screening is generally not cost-effective,[7–9] but this is based on assumptions (eg, labour costs of screening are high, risk of blindness without screening is only moderate due to a reasonably accessible health-care system) that apply far better in high-resource settings than low-income and middle-income countries such as China, where around 80% of the global burden of glaucoma blindness falls. Our article challenges this by looking carefully at a well documented screening programme in China, complemented by the fairly complete literature on glaucoma epidemiology that exists in China. We feel this novel finding in China might result from a combination of lower screening costs and higher risk of eventual blindness in the absence of such programmes in the Chinese setting compared with high-income countries. It is also likely that the greater cost-effectiveness of screening for PACG, which is far more prevalent in China than in European-derived populations, plays an important role.

Thus, results from our models are more likely to be applicable where labour costs are lower and risk of blindness in untreated people is especially high—eg, in low-income and middle-income countries, and especially those settings where highly blinding forms of glaucoma (PACG in east Asia and POAG in African-derived populations in sub-Saharan Africa and the Caribbean) are prevalent. Regarding the necessity of expensive technology for successful screening, which might present a barrier in such settings, we deliberately omitted consideration of costly approaches such as visual field analysers, gonioscopy lenses, and nerve fibre layer analysis to posit a screening model with broader applicability. The approaches modelled here are likely to be particularly relevant in Asia, where it is estimated that 61% of people living with glaucoma globally reside, and where cost-effectiveness of glaucoma screening has not been widely examined.[1]

Due to low expected compliance in China with hospital referrals from screening and with medical and laser therapies, we found in both rural and urban settings that each additional screening had the potential to identify additional people with early-stage glaucoma, and that more frequent, annual screening was the best strategy. However, when adherence was assumed to be perfect—an unlikely assumption in view of the extensive literature—annual screening was unnecessary and screening every 2 years became the optimal strategy. With inadequate knowledge of glaucoma, patients and doctors in China generally perceive no need for comprehensive examinations to detect asymptomatic disease.[62] Available evidence suggests that offering free examinations can improve acceptance of comprehensive examinations among asymptomatic patients in rural China.[63] Full coverage of such examinations under the national health insurance system could assist with opportunistic, clinic-based case detection of glaucoma. However, supporting broad-based population screening would require a substantial financial commitment from the government, which further research in this area might help to promote.

Our study has various strengths. To our knowledge, it is the first to analyse the cost-effectiveness of glaucoma screening in a low-income or middle-income country on the basis of a temporally explicit Markov model. Costs of screening and treatment were adopted from actual screening programmes and health-care facilities in China. Our analysis employed prevalence and transition probability estimates based on the globally recognised ISGEO classification system and a careful review of the published literature. Our policy-relevant conclusions about the cost-effectiveness of glaucoma screening differ substantially from much of the existing literature, especially studies in high-resource countries, due to China's unique characteristics, including relatively low screening costs and high probability of eye damage among unscreened persons, especially those with PACG.

A limitation of our study is that gaps in the existing literature required us to base some transition probabilities among health states in our Markov model on non-Chinese data, leading to potential inaccuracies. Also, our analysis was not informed by prospective data from a randomised controlled trial. The use of the WHO cost-effectiveness threshold for cost per year of blindness avoided is consistent with previous studies, but it is unclear whether the WHO thresholds are generalisable to disease-specific outcomes or QALYs.[9] The rural–urban comparison was done for illustrative purposes because the rural and urban GDP were calculated from overall GDP adjusted for income disparity in both settings. Although screening in urban areas might seem more cost-effective than in rural areas, such screening should be offered to both rural and urban residents for equity reasons. Further, we did not stratify our analyses by sex. Neither was the cost-effectiveness of different screening strategies compared in our study. In the absence of Chinese data on compliance with glaucoma medications, we based our estimates on studies of other chronic conditions, such as diabetic retinopathy and hypertension.

Because adherence to hospital examinations and medical and laser therapies is low in China,[6,16,64] there is substantial room for future studies to investigate the potential effects on adherence of various behavioural, economic, and educational interventions.

In conclusion, combined population screening for POAG and PACG among Chinese adults aged 50 years or older is likely to be cost-effective in both rural and urban settings. Our findings were insensitive to variations across a wide range of input parameters and were robust in the probabilistic sensitivity analyses. These results are more likely to be applicable in other settings where labour costs are low, highly blinding forms of glaucoma are prevalent, and opportunistic detection rates are low. A sustainable model might be for Chinese hospitals to offer free glaucoma examinations to residents living in local villages and communities that, under present funding arrangements, could increase the number of glaucoma inpatients and in turn increase their profits. Future studies should investigate the effectiveness of interventions among screened people to improve their compliance with hospital examination and acceptance of definitive care.

Contributors

YL, NC, CO, and FK conceived and designed the study. JT, JJ, and YL collected data used for the analysis. JT did the statistical analyses and drafted the initial manuscript. All authors commented and revised the manuscript critically. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of interests

We declare no competing interests.

Acknowledgments

We thank Hua Zhong of the First Affiliated Hospital of Kunming Medical University, Kunming, China, for sharing his unpublished data regarding the transitional probabilities of primary open angle glaucoma. NC is supported by the Ulverscroft Foundation (UK). YL is supported by the Wenzhou Medical University Research Fund (QTJ13009), Zhejiang Province Health Innovation Talents Project (2016025), and Wenzhou's Ten Major Livelihood Issues 2015.

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